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OBSERVATIONS

on the NATURE and TREATMENT of

EXOPHTHALMIC GOITRE

by

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There is perhaps no subject in the whole of Medicine upon which more extensive and laborious research has been undertaken than that of Exophthalmic Goitre. The problem which the cause and cure of this disease presents is one which commends itself to Pathologist and Clinician alike, and probably for two reasons: the condition is such a definite clinical entity; and the elucidation of its converse Myxoedema has resulted in such brilliant therapeutic success, as to perhaps encourage the hope, that were the fundamental nature of Exophthalmic Goitre but properly understood, its correction might be just as simple and as satisfactory. It cannot be said, up to the present, that /

that the results obtained are commensurate with the labour expended, but nevertheless very considerable progress has been made; and each advance in knowledge has only served to show how vast is the subject of the influence of the internal secretions on the general metabolism and on the maintenance of the vital functions. The problem is still further complicated by our scanty knowledge of the ductless glands other than the thyroid, for there is abundant evidence that their functions are mutually influenced, and that for the proper comprehension of any one of them, its relationship to the others requires to be fully known. The investigation of all of them then must go on together.

After several years first of hospital, and then of general practice in Nottinghamshire and Derbyshire - a district in which Exophthalmic Goitre is prevalent - the writer was impressed with the unsatisfactory state of our knowledge concerning the thyroïdal apparatus, and the treatment of its disorders. Indeed, the general management of Exophthalmic Goitre appeared simply to consist in rest /

rest in bed, attention to hygienic considerations and surroundings, and the palliative treatment of symptoms, - but a large industrial practice is not conducive to personal investigation.

The object of the present thesis is to present concisely a summary of recent research upon the thyroid gland, in so far as it is applicable to Exophthalmic Goitre, and to see what data are available to explain the etiology and clinical features of this disease. The investigations of McCarrison on the subject of Endemic Goitre, and of Kendall into the chemical composition of the thyroid secretion, have opened up a new field of thought, which in some measure may influence existing views on the Exophthalmic variety of Goitre; and there have been recorded a number of instances where treatment, instituted along the lines which consideration of these researches indicate, has been followed by more or less success, - sufficient at least to encourage further trials.

Abnormality of the thyroid secretion, both as regards quality and excessive quantity, was until recently regarded as being the primary and essential factor in the production of Exophthalmic /

ophthalmic Goitre. The recent investigations referred to, together with others of an experimental nature, which will be referred to later, have rendered this view somewhat doubtful; they seem to indicate rather that while it is one of the most important features of the disease, the thyroid perversion is a manifestation only - a symptom -, and the direct outcome of some other more obscure factors. Contrary to former belief, it has recently been shown that while a certain number of the symptoms of Exophthalmic Goitre are due to thyroid excess, and can be produced experimentally by over-feeding with the gland, there are others which cannot be explained in this manner, and for which some other cause must be sought.

It is proposed here to consider in turn the various symptoms of Exophthalmic Goitre, correlating to each the experimental and other work which may explain their origin; thereafter to discuss the subject as a whole; and finally to refer to any methods of investigation and treatment which logically may have been suggested by the work reviewed. It may however be convenient first to outline certain general facts concerning the /

etiology of the disease.

Prevalence and Distribution.

Exophthalmic Goitre is stated to be more prevalent at the Sea Coast. McCarrison states that it is very rare among the indigenous inhabitants of the Himalayas where endemic goitre is prevalent; this is said not to be the case in France, Switzerland, and in the region of the great lakes of North America. My own experience in Derbyshire and Nottinghamshire - a district where simple goitre is so frequently seen - undoubtedly supports the latter view.

Heredity. There is without doubt a family predisposition to the disease, and it is frequent to find two or more suffering from the complaint in the same family; or we may have one member of the household suffering from simple goitre, whilst another is the subject of the exophthalmic variety. In such families neuroses and psychoses often occur: while the children of women who suffer from Graves disease are very frequently abnormal in some way.

Age. The malady is seen chiefly between the ages of puberty and the menopause, though it may arise at /

at any period of life. Children under 12 years of age are rarely affected though cases have been recorded in infancy. Complete recovery is said to be more likely in young children.

Sex. The disease is approximately ten times more common in women than in men. In females it is almost entirely confined to the period of sexual activity, though it may, but rarely, occur after that age. In males it develops at a somewhat later period. One case which came under my notice a few months ago at the Edinburgh Royal Infirmary was in a man of 52 years of age - an unusual time of life for the disease to originate. From statistics it is shown that the onset is relatively later in the well-to-do than in the poor. The ages respectively in the poorer classes are, in the case of females, 15 to 30 years, and in the case of men 30 to 35 years.

The disease may show itself first during pregnancy or after parturition. On occasions, recovery or improvement has followed pregnancy. In a case described by Dr Boyd of Hillsborough (B.M.J. Aug. 9, 1919) a woman who suffered from goitre was during labour seized with intense dyspnoea /

dyspnoea and her condition appeared critical but after parturition was completed all the alarming symptoms passed off.

CLINICAL FEATURES:-

1. Enlargement of the Thyroid:-

This is a usual but not invariable feature of the disease. In most cases the degree of enlargement is moderate, and uniform; the gland is tender, smooth, and firm to the touch, and shows marked evidence of pulsation. This arises principally from the vessels within the gland itself, for it is extremely vascular, but to some extent it may be transmitted from the adjacent carotid arteries. The pulsation is palpable as well as visible, and in some instances a distinct thrill may be appreciated by the fingers. A systolic bruit is commonly to be heard on auscultation. This murmur is not obtained in simple goitre but is present in from 80% to 90% of cases of the exophthalmic variety, and is therefore of great diagnostic value. For this reason if a bruit be audible over an enlarged thyroid other signs of exophthalmic goitre should be sought for if the case be at all obscure. The extreme vascularity of the thyroid is shown by the fact /

fact that its size can be temporarily reduced by squeezing: it is also abundantly appreciated from the profuse haemorrhage, which is an invariable accompaniment of any operative procedure on the gland. The severity of the disease cannot in any degree be estimated by the thyroid enlargement, for in exceptional cases, although other symptoms quite characteristic of Exophthalmic Goitre may be present, the thyroid may show no appreciable increase in size; nor does it follow that because enlargement is absent that the function of the gland is not deranged, as in these cases extensive alteration in structure has sometimes been demonstrated. The size of the gland is dependent upon the state of the general nutrition and upon the individual's power of response to stimuli affecting the thyroid, as well as on the degree of virulence and constancy of action of the exciting agent. It must also be kept in mind that in some instances the gland is enlarged retrosternally, - a fact which it is often extremely difficult to appreciate by the ordinary methods of examination, - or that accessory thyroids may be present and affected.

Histologically, /

Histologically, there is found a hyperplasia affecting the whole organ, together with a great degree of lymphocyte infiltration. The epithelium lining the glandular spaces shows greatly increased activity, and there is a characteristic absence of the normal colloid material, a mucoid substance being formed in its stead. However, if it should happen that the hyperplasia is superimposed on a colloid goitre, then colloid substance may be found in the thyroid owing to its retention in the vesicles by fibrous overgrowth and lymphatic stenosis. It has been shown that there is produced in the gland a substance which has a powerfully depressant action upon the blood pressure: this will be referred to later.

The degree of thyroid enlargement may vary from time to time during the disease. The gland may become temporarily increased in size after excitement or exertion, and at the menstrual period: or it may slowly and steadily increase for a time and then gradually diminish - a process which may be repeated in alternation. Occasionally with its temporary diminution in size a slight transitory improvement in the disease is noticed. The whole gland may be involved or one lobe may be more /

more affected than another, or areas of hyperplasia may be disseminated throughout an otherwise healthy gland.

Observations upon enlargement of the thyroid in general:-

Enlargement of the Thyroid due to Thyroiditis may occur as a result of some acute infectious disease of bacterial origin such as a Tonsillitis or some other Fever. The increase in size in these cases is often extremely rapid - a few hours - and may occur early in the course of the primary illness. This would at once suggest some connection between the bacterial infection and the thyroid enlargement, although the protective role of the gland in acute diseases must not be forgotten. In most cases the enlargement rapidly subsides, with the decline of the infection, though a few cases are on record where a Thyroiditis originating in this manner, has apparently been succeeded by a true Exophthalmic Goitre. It would seem reasonable in these cases to suspect that the bacterial agent had played some important part in determining its onset, and that it possibly might be the specific cause.

The extensive investigations of McCarrison
on /

on the subject of Endemic Goitre have shown conclusively that bacterial infection plays a part of paramount importance in its production: that such bacterial infection is derived most commonly from the gastro-intestinal tract: and that the original source from which the infective agent is derived is an impure water supply, the impurity being acquired from soil contamination. His experiments have also shown that the thyroid enlargement can be induced artificially in animals by continued feeding on substances contaminated with faecal or other bacterial-bearing material; whereas prolonged thyroid-feeding is not followed by any increase in the size of the gland. Both the Endemic and the Exophthalmic varieties of Goitre have this in common that they tend markedly to occur in certain districts, while others are practically clear from them; though the available evidence seems to show that they do not usually occur in association. It would seem reasonable therefore to follow out with regard to Exophthalmic Goitre the same line of research which he used in investigating the Endemic form. One great difficulty however in all experimental work on this disease is that no condition is met with among the lower animals /

animals, which exactly corresponds to it. It seems that the disease is one peculiar to the human species, - at any rate so far as the entirety of its clinical features is concerned. It would seem therefore, that however much to be desired, animal investigations on the subject of Exophthalmic Goitre are likely to yield disappointing results.

McCarrison mentions the occurrence of cases where the Exophthalmic variety of Goitre has followed upon the Endemic: though the data given are insufficient to justify speculation as to the relationship, if any, of the one to the other.

Apart from tumours, abscess, and parasitic conditions, the above data are apparently the sum of our knowledge of the factors which bring about thyroid enlargement. All that can be definitely asserted at present, is that in both Thyroiditis and Endemic Goitre, the primary factor is apparently a bacterial infection.

2. Exophthalmos:-

Protrusion of the eyes is one of the most striking features of the disease, and the one which imparts to the patient that appearance which is /

is so characteristic. Like the thyroid enlargement, Exophthalmos is not present in every case. As a general rule however, it will be found in some degree in the majority. Its onset is usually somewhat gradual, and it often appears later than many of the other symptoms: it may however become rapidly established, and occur early in the disease. It is the rule for both eyes to be affected equally, but occasionally one only becomes protruded; it has been pointed out that this unusual form of Exophthalmos is sometimes associated with unilateral enlargement of the Thyroid. In extreme degrees of Exophthalmos the eyelids may not meet during sleep.

Dependent upon the Exophthalmos there are a number of associated 'lid signs', but as these do not affect the investigation as here outlined, their detailed description may be dispensed with. The principal ones may be mentioned in passing! -

1. Rareness of involuntary winking.
2. Failure of the upper lid to follow the eyeball during its downward movement.
3. Weakness of convergence of the two eyes.
4. Absence of wrinkling of the forehead when the patient looks upwards.

The pupils of the eyes are usually much dilated. There has also been described a phenomenon - the converse of the Argyle-Robertson - in which the pupils react to light, but show no alteration on accommodation. From their prominence, the eyes are peculiarly liable to external irritation, and ulceration of the cornea or conjunctivitis are not infrequent accidents. In extreme cases of corneal ulceration, the eye may become so destroyed as to require enucleation. A severe case of this description came under my own observation, while in practice in England. The ulceration of the cornea was so extensive as to result in sloughing of that structure with eventual perforation: this was followed by panophthalmitis and finally by total destruction of both eyeballs, necessitating a double enucleation.

The exophthalmos bears no relationship to the severity of the disease. It varies greatly at different times. If the patient is quiet it may be scarcely noticeable, but under slight mental excitement it may become a prominent feature. The patient often complains of a sense of straining of the eyes and sees flashes of light. There is occasionally weakness and paralysis of various ocular /

ocular muscles; this is probably simply a feature of the general muscular weakness. Watering of the eyes and epiphora have been noted as initial symptoms in some cases. Pigmentation, so common in this disease, may show itself very distinctly on the eyelids. Vision is not affected.

Observations upon the production of Exophthalmos:-

The precise mechanism by which Exophthalmos is produced has been a matter of considerable dispute. An increase of intra-orbital fat is frequently found post-mortem, but this appears to be a secondary deposit only. The increased vascularity of the vessels of the orbit may be contributory. It appears however that the Exophthalmos is mainly dependent upon spasm of the Levator Palpebrae Superioris, and of Muller's muscle. This together with the dilated state of the pupil would suggest at once involvement of the sympathetic system, and some interesting experiments and observations have been made in this connection.

Division of the Sympathetic in the neck is followed by disappearance of the Exophthalmos, and this procedure is sometimes resorted to surgically /

surgically for the purpose of improving the appearance in inveterate cases, or of lessening ocular irritation. Conversely electrical stimulation of the divided sympathetic produces Exophthalmos. Continuous excitation of the sympathetic has been produced in cats by junction of the phrenic nerve with the peripheral portion of the cut cervical sympathetic: this was followed by Exophthalmos upon the operated side.

Exophthalmos is not the result of excessive thyroid secretion: it may develop even after removal of the entire gland, or if previously present may persist after operation. Nor has the condition been reproduced by excessive thyroid feeding either in animals or in man, - with the possible exception of one instance in which mice were given enormous quantities (in proportion to body weight), and in which the results were doubtful. All other experiments along these lines appear to have been definitely negative.

It has been suggested that Exophthalmos is the direct result of over-activity of the adrenal bodies. One argument however against this view is that in Exophthalmic goitre the blood contains a substance which powerfully lowers the blood pressure /

pressure, whereas the adrenal secretion has exactly the opposite effect. Be that as it may, there is no doubt that an intimate relationship exists between the sympathetic system and the adrenal bodies. Indeed the two sets of structures are commonly regarded as associated, and together to form one system - the adrenal-sympathetic. It is also known that increased activity of the adrenals is an accompaniment of sympathetic excitation. It is just possible, though as yet there is no evidence to prove it, that continuous outpouring of excessive adrenal secretion may in the long run bring about a change opposite to that usually produced, and that whereas in small quantities and over a short period of time the adrenal secretion brings about a rise in the blood-pressure, yet its continued out-pouring in large amount might in time bring about an actual fall. This indeed is the case with the secretion of the pituitary, a single dose producing a rise in blood pressure, while subsequent doses bring about a fall. It is probable however, according to certain observers, that the depressor substance referred to is elaborated in the intestinal canal.

Actual atrophic changes have been observed in the adrenal bodies in a few cases. The pigmentary changes /

changes in the skin, so frequently associated with Exophthalmic Goitre, provide another feature which further suggests relationship between this disease and the adrenal bodies. It has also been noted that Glycosuria occurs easily, and a predisposition to this might be the result of increased adrenal secretion, - as it can be experimentally induced by its administration.

From the observations above detailed, it would appear fairly certain that the increased activity of the thyroid and the production of Exophthalmos are independent one of the other, when viewed in the light of cause and effect. Their frequent association together however seems to render only reasonable and probable the assumption that the cause which produces the one set of changes is also responsible for the other. In other words, that both owe their genesis to the same exciting agent.

3. Tachycardia:-

Tachycardia is one of the most constant symptoms of Exophthalmic Goitre, and amongst the earliest to appear. The pulse rate is seldom under 100 beats per minute, in a well-defined case, even when the patient is at rest: it is further extremely /

ly unstable, and becomes rapidly much accelerated upon the slightest excitement or exertion, especially by the former. Any excitement may induce an attack of acute tachycardia, in which the pulse rate may reach 200 beats per minute, or even more. This complication is associated with a sensation of great uneasiness over the heart, and a feeling of suffocation, and a fatal outcome is not very uncommon. Constant rapidity of the pulse while a patient is at rest in bed should always raise the suspicion of a possible Exophthalmic Goitre, even in the absence of other physical signs and symptoms. Palpitation is the usual accompaniment of tachycardia, and is therefore one of the commonest features of the disease. The action of the heart may be regular or irregular. Irregularity points to an unfavourable prognosis. The heart beats may sometimes be heard while standing at the bedside, and indeed in a case which I had under my care in the Midlands of England, the Mother assured me she could hear it at night, when all was quiet, at the bedroom door. I had no means of verifying the accuracy of this statement. Examination of the heart shows that this organ is usually both hypertrophied /

hypertrophied and dilated. Systolic murmurs are usually to be heard in both the mitral and tricuspid areas: these are generally the result of relative incompetence of the valves from dilatation, but organic disease of the heart is by no means uncommon in these cases, - a point which was much emphasised by the late Professor Greenfield in his teaching. The pulse resembles in character that of aortic incompetence. There is usually "leaping" of the blood vessels - even in those of the retina - Synchronously with the beating of the carotids there may be a nodding movement of the head. The pulsation may sometimes also be appreciable in the liver and spleen.

Observations upon the production of Tachycardia:

Thyroid feeding in animals is not followed by any increase in the pulse rate. In man however the effects are different, for administration of the gland is followed by acceleration of the pulse, and indeed when the substance is being used medicinally, the pulse is the principal index whereby the dosage can be gauged. The effects however vary greatly in different individuals: a few grains in a susceptible subject may bring about extreme /

extreme acceleration, whereas one of greater tolerance may take ten grains or more daily over long periods without much effect on the circulation. Possibly the difference of this individual reaction may be explained by the most interesting observation of Kendall, who found that in animals if a-Iodine were administered by itself tachycardia did not result, but that if amino-acids were injected at the same time the pulse rate became enormously accelerated. It would thus seem reasonable to infer that the proportion of these formed in any particular person would be an important factor in determining the action of the thyroid secretion. Amino-acids in the human subject are the products of intestinal decomposition, and are particularly derived from the protein elements of the food. It has further been pointed out that tachycardia is more likely to follow thyroid administration in cases where the normal secretion of the gland is defective in amount.

It seems therefore that in the human subject, it is the thyroid secretion - whether normal or abnormal - that plays the most important part in the production of the circulatory symptoms of /

of Exophthalmic Goitre. Other factors however are probably in some degree contributory. Irritation of the sympathetic undoubtedly plays a part; and it is possible that the perverted thyroid secretion may exert a deleterious effect upon the heart itself, and this would explain the not infrequent occurrence of organic valvular disease. Less important factors are the general dilatation of the arterial system, and the increased processes of metabolism. The direct action of some toxin on the heart is also suggested by post-mortem findings of fatty degeneration and brown pigmentation, together with a variable degree of arteriosclerosis.

The increased circulatory activity furnished the explanation of a number of the minor manifestations which accompany Exophthalmic Goitre. Examples are the flushing of the skin, the subjective sensations of heat, the excessive activity of the sweat glands, and the tendency to dermographia, - all of which are usually present in some degree.

4. Tremor:-

Nervous symptoms of greater or less degree are to be found in all cases. Of these tremor is the commonest and most important, so much /

much so that it is regarded as one of the cardinal signs. This tremor is fine in character - from 8 to 10 to the second - and is seen particularly in the fingers. It can often be better appreciated by the touch, than by the eye and is more noticeable when the patient is excited or standing. The tremor may also be apparent in feet and tongue, or it may affect the whole upper extremity as well as the legs: it occasionally is unilateral. "Attacks of trembling" may affect the whole body. Delicate movements only may be involved, and one frequently finds that a patient writes, sews, or buttons his or her coat with difficulty, but may be quite able to steadily convey a glass of water to the lips. The tremor is not reproduced in animals by thyroid feeding, but may be seen in the human subject in similar circumstances. In Goitre it is at least in part due to the extreme degree of muscular weakness by which the disease is accompanied.

The patient is easily fatigued, extremely excitable mentally, and suffers from feelings of unrest, apprehension, and anxiety. The mind is as easily fatigued as the body, and the patient is emotional and often irritable. Headache and sleeplessness may be troublesome, and these are apparently /

apparently accounted for by the cerebral hyperaemia consequent upon the dilated state of the arterial system, though toxæmia of any kind is another possible cause. In some cases, the mental symptoms may assume a more exaggerated form, - so much so that actual insanity may occur. This may take one of a number of forms from melancholia to mania, or may be of the delusional variety similar to that observed in Myxoedema.

The disease is from time to time associated with other nervous diseases, either in the patient herself or in other members of the family. Thus we may have a history of chorea, hysteria, or epilepsy. Nervousness is always a prominent feature and many of the symptoms of neurasthenia are present in Exophthalmic Goitre, i.e. headache, flushings, tremblings, tachycardia, diarrhoea, sleeplessness and irritability etc. Fright and shock are causes of neurasthenia as well as of Exophthalmic Goitre and it is interesting to observe the similarity between fear and Graves disease. When a person is subjected to intense terror we get an almost true picture of Exophthalmic goitre, i.e. tachycardia, violent palpitation, trembling of the muscles of the body: the eyes start /

start forward and gaze at the object of fear; the skin is cold and clammy; the intestines are affected, producing diarrhoea; and we may even observe an enlargement of the thyroid gland. From these considerations it appears to me that on occasion abortive or undeveloped cases of Exophthalmic Goitre may be misdiagnosed as "Neurasthenia".

It has been stated that Exophthalmic Goitre was frequent in soldiers during the recent war. It may have been, but that was not my experience. Indeed during the whole of my time with the Royal Army Medical Corps I did not see one single instance. Certainly there were no examples of sudden onset amongst the troops under my charge. It is quite likely that some cases which were diagnosed as Exophthalmic Goitre were in reality cases of tobacco poisoning, especially if the patient had a simple goitre. The use of tobacco was carried to an extreme degree and very frequently among men of so youthful an age that they could not have been accustomed to the drug. The tremors of tobacco poisoning and those of Exophthalmic Goitre are very similar, and certainly/

ly the experiences of men in the trenches could very easily account for the nervous symptoms, especially when the subjects were already pre-disposed by the toxic effects of tobacco.

A number of changes have been reported as present in the nervous system on post-mortem examination. The findings however appear to be contradictory, and it cannot be said that any of the changes are constant or characteristic, and there is no evidence available to justify decision as to whether they are primary or secondary. Their inconstancy would point to the latter explanation, if indeed they are really definitely associated with the disease, and not due to other causes. Areas of softening or sclerosis in the brain and medulla, very minute haemorrhages (Greenfield) and degenerative changes in the sympathetic ganglia, are the most important of the changes described.

The increased excitability of the sympathetic nervous system has been already noted as one of the most characteristic features of the disease, and apparently accounts for the increased functional activity of the heart, glands, intestine, and respiratory apparatus, as well as in part for the alterations in metabolism.

5. Metabolism in Exophthalmic Goitre:-

The /

The influence of the thyroid on the body metabolism is very profound. The absence of its secretion, or its insufficient production, are followed by a general retardation of the processes of metabolism, as seen typically in cases of Myxoedema. On the other hand, where the secretion is present in excess, all these processes become exaggerated, and are performed much more rapidly than in the normal individual. This increase of metabolism is chiefly seen as affecting the protein elements: their consumption is on a very much extended scale, and as a result the excretion of nitrogen, urea, uric acid and phosphates is considerably augmented. The elimination of Sodium, Calcium, Magnesium, and Phosphorus is also stated to be greater than in the normal individual. On the other hand, the power of assimilation of both fats and carbohydrates is lessened, and Alimentary Glycosuria is likely to arise from any excess of the latter. True diabetes, from organic changes in the pancreas has been noted in rare cases. Polyuria is not uncommon, and there is great general loss of fluid. The respiratory exchanges are stated to be increased /

creased from 50% to 80%.

A number of features of the disease result from this increase in the metabolic processes. There is increased heat production, and it has been suggested that calorimetry affords the most accurate means of estimating the severity of the disease, and its progress under treatment. This method however is not one that can be applied in ordinary practice, owing to the special apparatus required. The increased heat production may afford an explanation of the subjective sensations of heat which are commonly complained of, and also of the irregularities of temperature that are met with. Loss of weight is another sequence of increased metabolism, and is a practically constant feature of Graves' Disease. The patient may lose two or three stones or more and if the emaciation is extreme the prognosis is unfavourable. Alterations in the skeleton occur as a result of the changes of 'salt' absorption. The bones may become softened and decalcified, and even Osteomalacea may be developed. If the goitre be acquired in early life, the skeleton may remain slender. A commonly noted bony alteration is wearing down of the crowns of the teeth.

The alterations in metabolism, which occur
in /

in Exophthalmic Goitre, are apparently the direct result of the increased thyroid secretion. They can be reproduced experimentally in animals from excessive dosage with the gland extract, and are seen in the human subject under treatment with the same substance. Pronounced loss of weight is produced in cases of Myxoedema whenever the patient is brought under the influence of Thyroid, and this affords one of the first signs of recovery. Use also is made of this action of Thyroid in the treatment of Obesity, and the drug is one of those most commonly employed for the cure or amelioration of this disease.

The foregoing five features of Exophthalmic Goitre are those which play the most important part in its clinical picture, and upon which most research has been carried out. There are however two minor symptoms, which may be briefly referred to, as they may shed a certain amount of light upon the mode of origin and pathology of the disease, and also serve to suggest certain lines of treatment, which might possibly prove of value.

6. Gastro-intestinal Disturbances:-

Derangement /

Derangement of the digestive tract is a not uncommon precursor of the onset of Exophthalmic Goitre, and in a fairly large proportion of cases, the stomach will be found dilated. The gastric juice is frequently deficient in organic acid, and as in all other conditions in which hypoacidity occurs, the growth and multiplication of micro-organisms is thereby favoured. Dyspepsia in some form or another is a frequent precursor of the disease: some cases start with an acute attack of vomiting and diarrhoea: in others, intestinal stasis has been long present. In some of my notes I find the account of a case which was admitted into the hospital, at which I was then acting as Resident House Physician. The patient was suffering from well-marked Exophthalmic Goitre. Her history was that she had for many years been troubled with periodic attacks of diarrhoea, most commonly in the mornings. These occurred about once a week and were accompanied by pain in the right iliac region and in the back. Her condition had been variously diagnosed as chronic colitis etc. Unfortunately I was unable to follow the case to its conclusion as my term of office expired, but it seems to the writer that the eventual /

eventual Exophthalmic Goitre may have been a remote sequence of the intestinal condition. Acute gastro-intestinal symptoms may be produced in animals by feeding with thyroid, and the secretion of the gland appears to play a considerable part in the production of these symptoms in the human subject, but it does not appear to be the only possible factor in their etiology. Degenerative changes in the liver and pancreas have been observed post-mortem. The effects of treatment seem to indicate that in certain cases at least, the disease owes its primary origin to some derangement of the gastro-intestinal tract: these will be referred to later.

7. Persistence of the Thymus:-

Persistence of the thymus is a very constant occurrence in cases of Exophthalmic Goitre, and there is a general increase of lymphoid tissue throughout the body. Little is usually known about disease in which increase of lymphoid tissue is a prominent feature. The two most notable examples are Hodgkin's Disease and Leukaemia: both of these are supposed to be due to some chronic infective agent, but there is very little definite information as to their origin. McCarrison mentions /

mentions that in pigeons septicaemia is followed by atrophy of the thymus, and suggests that a minimal action of bacteria might account for the production of thymus enlargement.

A consideration of the facts which are known concerning the mode of onset, the symptoms and signs of Exophthalmic Goitre, and of the various experiments which have been performed with the object of its investigation, seem to show

1. That certain of the features of the disease are due in whole or in part to excess of thyroid secretion.

2. That others, - and some of them the most important and constant - cannot be so explained. Of these many are dependent upon increased excitability of the sympathetic nervous system, but by what means this change is brought about is not as yet apparent.

3. That the disease is one peculiar to the human species, and that its investigation is greatly impeded because of the impossibility apparently of reproducing it in animals.

4. That the disease presents certain features, in its mode of onset and in its minor symptoms, which /

which suggest that bacterial infection or the products of bacteria may be the possible primary cause. This view is supported by the analogy of Endemic Goitre, and also by the effects of treatment shortly to be discussed.

Evidence obtained from Treatment, as to the Etiology of Exophthalmic Goitre:-

An experiment of Kendall, already referred to, showed that in animals tachycardia was not produced by the administration of a-Iodine alone, but that if amino-acids were injected simultaneously, enormous acceleration of the pulse rate followed. Amino-acids are toxic substances derived from bacterial decomposition, which takes place within the intestinal tract. These it is stated may act directly upon the adrenal-sympathetic system, and so would - in conjunction with excessive thyroid secretion - afford an explanation of many of the features of Exophthalmic Goitre. Their presence in the blood would be a matter of some difficulty to prove. Sanford and Blackford however have found in the blood a powerful depressor substance, which they state is comparable in its action to 10% peptone, and is probably derived from the gastro-intestinal /

gastro-intestinal tract.

Following up the line of treatment suggested by a possible condition of intestinal toxæmia, certain remarkable results have been recorded. The cure of intestinal stasis, either by operative (Lane) or medicinal methods (Ebstein) has been followed by the disappearance of the symptoms of Exophthalmic Goitre, though in Lane's case enlargement of the thyroid persisted. In cases where the onset was preceded by a condition of chronic colitis the efficient treatment of this latter was followed by a very great amelioration of the Goitrous symptoms. (Hemmeter). Since its first suggestion by McCarrison for Endemic Goitre, Thymol has been frequently used in the Exophthalmic variety. Its action is that of a powerful intestinal antiseptic, and the doses in which it is used are large - ten grains night and morning in cachets. During its administration, oils and alcohol which are solvents for the drug, must be avoided, - as otherwise toxic symptoms might be produced. It is difficult fairly to estimate the action of any drug in a disease like Exophthalmic Goitre, where improvement, at any rate temporarily, results from rest / .

rest in bed and the other accompaniments of hospital regime. Nevertheless in a number of cases, its use appeared to be followed by considerable benefit, and the patient themselves stated that they felt improvement.

There are of course other possible sources of bacterial infection, besides the gastro-intestinal tract. The onset of Goitre after Tonsillitis and other Fevers may connect its causation with their occurrence. All possible sources of sepsis must be kept in mind, and every system of the body requires to be most thoroughly investigated. The toxins of 'Rheumatism', Tubercle, and Syphilis are said to be responsible in certain cases - at least there is a history of their previous occurrence of these diseases - and this should always be enquired into.

THE BLOOD IN GRAVES DISEASE. -

Recent literature emphasises the importance of examining the blood in Graves Disease, as information may thereby be obtained as to the severity of the disorder. According to Marine and/

and Lenhart, there is 'a close parallelism between the percentage of mononuclears in the circulating blood and the extent of active lymphoid and thyroid hyperplasia', and this percentage 'is a fair index of the severity of the disease'. If this is so, then the importance of blood examination cannot be exaggerated.

In a case which came under my notice in one of the Wards of the Edinburgh Royal Infirmary, a few months ago, the following was the result of the leucocyte count:- There was a definite leucopaenia. The polymorphonuclear leucocytes showed a diminution to 50%. The lymphocytes, both large and small, were distinctly increased, and together made up about 47% of the cells. This corresponds in the main to the findings of other observers.

These changes in the blood are also seen in cases of Simple Goitre, Myxoedema, various intoxications, and in intestinal disorders.

CLINICAL TYPES of EXOPHTHALMIC GOITRE.

It will be apparent from their discussion that the symptoms of Exophthalmic Goitre are /

are very variable in their occurrence and in their degree and, therefore considerable diversity of clinical picture may be produced. Thus various types of the disease may be differentiated. When the disease has full complement of pathognomonic symptoms and signs, it is said to be complete. Incomplete types often show little more than extreme nervousness with Tachycardia. Acute and Chronic cases have been described . The acute forms may pass off in a few days thus Moore has reported a case in a girl who recovered in two days. Other cases have been recorded which were restored to health in from two to six weeks. A chronic case may commence acutely or may have acute symptoms superadded from time to time. The duration may last for many years. Then again a thin type and a fat type have been described. Those who are well nourished usually do better than those who show emaciation, ^{but} for in the case which came under my observation and which is elsewhere referred to and where destruction of the eyeballs resulted, the girl was well developed and of fresh complexion. Again the disease may be primary or secondary, the latter being superimposed upon simple goitre. Finally there has been described what is known as "false" exophthalmic /

exophthalmic goitre in which the symptoms resembling Graves Disease develop in a case of simple goitre, and result from effects of pressure on the sympathetic and pneumogastric nerves.

COURSE AND TERMINATIONS.

Statistics show that under medical treatment about 50% recover sufficiently to resume their former occupation, though they may not be able to devote to it such care and attention as before. On the other hand death may result from syncope, or other cause of cardiac failure; or from exhaustion owing to the severity of the gastro-intestinal disturbance, i.e. diarrhoea, vomiting, etc.; or again acute mania may lead up to a final termination. Death is very frequently preceded by marasmus and emaciation. Intercurrent disease on the other hand may be responsible - e.g. Pneumonia, Tuberculosis, Bronchitis. In a case of simple goitre described by Dr Boyd of Hillsborough (B.M.J. Aug. 9, 1919) death resulted from tuberculosis, and it was noticed that although there was extreme general emaciation there was no diminution in the size of the gland, which indeed became more noticeable owing to the wasting of the surrounding structures.

In cases which recover some evidence of
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the disease may persist for many years, e.g. slight exophthalmos, nervousness, or irritability of temper. In other instances it is found that after apparent recovery the symptoms reappear, following an acute illness, operation, or nervous shock. Relapses are very common, and it may almost be stated that they are the rule. Dr Haggard of Davos Platz has described a case in which relapse occurred whenever the patient left a high altitude. Although spoken of as "relapses" it is more likely that these are but recrudescences of the original illness which has been for a time quiescent. The more a patient taxes her physical and mental resources the more likely is 'relapse' to follow. On the other hand, if she is able to take complete rest from all forms of exertion and excitement the more probable is it that recovery will prove permanent. For this reason the outlook is better in one of the leisured classes.

Finally Exophthalmic Goitre may be followed by Myxoedema, the result of fibrosis or exhaustion of the gland leading to cessation of the secretion.

The Investigation and Treatment of Cases of Exophthalmic Goitre:-

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The patient should be examined with the utmost thoroughness and every system of the body carefully investigated. The previous history must be enquired into with care as it may give important information as to the possible exciting factor. Particular attention should be directed to the discovery and treatment of possible sources of Sepsis, for in the present imperfect state of our knowledge, the removal of these seems to offer the greatest hope of effecting a more or less complete cure. The teeth, tonsils, nasal sinuses, gall-bladder, appendix, and gastro-intestinal tract, should be particularly kept in mind as the most likely sources, unless the history of the mode of onset or previous illnesses of the patient suggest definitely any other. Where no particular cause is obvious, it is well to carry out a bismuth-X-ray investigation of the alimentary system before concluding that no abnormality is present. Indeed, even though nothing be found, there can be no harm in trying a course of intestinal antiseptics - particularly thymol -, and in practising intestinal lavage. A Wassermann reaction should also be done, where there is any reason to suspect Syphilis. In all cases a thorough examination of the faeces should be made - chemical and /

and bacteriological. The discovery and removal of any source of sepsis, seems at present to afford the only known means of obtaining possible cure though it is only recently that such a line of treatment-investigation has been put forward, and the recorded cases where it was followed by success are not as yet very numerous. Some of those are nevertheless of a very striking nature, and suggest that the method is well worthy of further trial. Personal experience has convinced the writer that this is so, but the opportunities of applying these principles in general practice are distinctly limited, owing to the comparative rarity of the disease.

The question of the advisability of surgical operation in Exophthalmic Goitre is one concerning which there is considerable difference of opinion, and individual views must vary according to the standpoint from which the disease is regarded. If it be considered that the disease is the result of thyroid activity entirely, then removal of the gland would appear to be rational, but if this be regarded - as most recent investigations seem to suggest - as a secondary manifestation only, operation would seem to be illogical.

Operations /

Operations upon the thyroid are attended by considerable danger, in part due to the surgical procedure itself, and in part to the anaesthetic, and there is a considerable mortality due to the interference. As a general rule, it seems now to be recognised that the results obtained do not greatly exceed in success those which follow ordinary medicinal treatment, and it is questionable whether they justify the additional risk which is entailed. Formerly operative treatment was much in favour: now it is much less readily advocated. The circumstances of the individual case can alone decide the question, and each must be considered on its merits.

The general medical treatment of Exophthalmic Goitre is largely of a palliative nature, though there are a few remedies which appear to exercise some more or less directly beneficial action upon the disease.

General Management:-

In severe cases rest in bed is essential, and by this means unaided, very considerable amelioration of many of the symptoms - especially the tachycardia and nervous excitability - will be brought about. In all cases as much rest and quietness as possible should be obtained, and all forms /

forms of excitement must be absolutely avoided.

The diet should be plain and one which as far as possible excludes meat: it should contain abundance of milk, green vegetables, and fresh fruit, and should be free from substances liable to produce intestinal fermentation. Buttermilk or artificially soured milk may be taken advantageously. Fish, fat bacon, chicken and eggs may be allowed. Tea and coffee are only to be given in moderation. Alcohol and tobacco must be absolutely forbidden.

Regular attention must be paid to the state of the bowels, though it must be stated that constipation is not usually a troublesome feature.

A change of air is often beneficial and as a rule these cases do well at a fairly high altitude. The change must be thoroughly restful and quiet and all necessary measures provided to ensure the patient's comfort.

Local applications to the thyroid:-

An ice-bag over the gland frequently gives good results. It may also be applied to the praecordia when there is troublesome palpitation. The application of weak red-iodide of mercury ointment over the goitre has its advocates.

Electricity /

Electricity does not appear to be of much if any benefit. Exposure to the X-rays gives variable results, but in some instances appears to be of very considerable value. Application over the thymus, ovaries, and adrenals, is also advocated by different observers. Radium treatment has similarly proved of benefit in a fair proportion of cases.

Medicinal Treatment:-

(a) Drugs which exert any direct beneficial action upon the disease are very few in number. Of these Neutral Hydrobromide of Quinine has been strongly supported, given in doses of five grains thrice daily. Its use is followed by a diminution in the size of the gland, a decrease in the pulse rate, and a diminution in the degree of sweating and of tremor. McCarrison suggests that its beneficial action is mainly due to its action as an intestinal antiseptic, and states that good results are usually seen within two months from the commencement of its administration. Iodine internally is recommended by the same author, in the form of Syrup of Iodide of Iron. He advises that the initial dose should be small, commencing with 5 minims thrice daily for a week, and then increasing /

increasing the quantity to ten minims. It is stated to cause a reversion of the thyroid to the colloid state, to increase its iodine content, and to bring about a diminution in the blood supply. Thymol and other intestinal antiseptics are advocated on the supposition - in favour of which there is a good deal of evidence - that perverted bacterial growth is at least a factor in the etiology of the disease, and encouraging results have been obtained from their employment.

(b) Where any possible exciting cause may have been detected drugs whose object is directed to its removal may be employed. Thus antirheumatic or antisyphilitic remedies may be required in special cases. The use of those required by intestinal or gastric disorders has been already mentioned.

(c) Certain remedies are generally regarded as useful in allaying particular symptoms which may call for treatment. Belladonna is advocated as both a cardiac and nervous sedative. Bromides and various hypnotics are often required where there is much mental excitement. Digitalis may be called for by cardiac failure. A substance/

stance isolated from the anterior lobe of the Pituitary, to which the name of 'Tethelin' has been given, is said to control the tachycardia, nervous manifestations, and the disordered metabolism (Robertson and Richter).

(d) Vaccines prepared from the intestinal flora are said to have given promising results in the few cases in which they were employed.

(e) Rodagen, - the dried milk of thyroidectomised goats - has been strongly recommended, but the results appear to be inconstant, though in a certain proportion apparently beneficial.

(f) Sera and animal extracts do not appear to be of much, if any, value, with the possible exception of preparations of the Pituitary.

Corpus Luteum may prove beneficial and under its influence the patient puts on weight.

(Eason) Amongst other drugs that have been recommended may be mentioned Convallaria, Potassium Iodide, Syrup of Hydriodic Acid, Iodipin, Phosphate of Soda, Calcium Chloride, and Cod liver Oil. If anaemia is present Iron should be given.

In conclusion, it may be said that the treatment /

treatment of Exophthalmic Goitre, as usually carried out, can be regarded only as far from satisfactory. The most promising results are apparently obtained in those cases where some source of sepsis is discoverable, and it is apparently along the lines of research indicated by McCarrison that most progress is likely to be made.

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